

d his

09/716,054  
Updated Search  
L/cock 4/7/06.

(FILE 'HOME' ENTERED AT 13:09:36 ON 07 APR 2006)

FILE 'BIOSIS, CAPLUS, EMBASE, MEDLINE' ENTERED AT 13:09:54 ON 07 APR 2006

L1 141 S PYEEI?  
L2 3 S L1 AND FK?  
L3 2 S L1 AND SLF?  
L4 2 S L2 AND L3  
L5 1 DUPLICATE REMOVE L4 (1 DUPLICATE REMOVED)  
L6 0 S L1 AND DALTONS?  
L7 0 S FKPYEEI  
L8 6 S SLFPYEEI?  
L9 0 S FKPYEEI?  
L10 2 DUPLICATE REMOVE L8 (4 DUPLICATES REMOVED)

FILE 'BIOSIS, CAPLUS, EMBASE, MEDLINE' ENTERED AT 13:21:16 ON 07 APR 2006

L11 50 S FKBP AND NFAT  
L12 8 S L11 AND RAPAMYCIN?  
L13 5 DUPLICATE REMOVE L12 (3 DUPLICATES REMOVED)

=>

ANSWER 1 OF 2 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

DUPLICATE 1

AN 2004:465119 BIOSIS

DN PREV200400460986

TI Quantitative analyses of bifunctional molecules.

AU Braun, Patrick D.; Wandless, Thomas J. [Reprint Author]

CS Dept Mol Pharmacol, Stanford Univ, Stanford, CA, 94305, USA  
wandless@stanford.edu

SO Biochemistry, (May 11 2004) Vol. 43, No. 18, pp. 5406-5413. print.

ISSN: 0006-2960 (ISSN print).

DT Article

LA English

ED Entered STN: 1 Dec 2004

Last Updated on STN: 1 Dec 2004

AB Small molecules can be discovered or engineered to bind tightly to biologically relevant proteins, and these molecules have proven to be powerful tools for both basic research and therapeutic applications. In many cases, detailed biophysical analyses of the intermolecular binding events are essential for improving the activity of the small molecules. These interactions can often be characterized as straightforward bimolecular binding events, and a variety of experimental and analytical techniques have been developed and refined to facilitate these analyses. Several investigators have recently synthesized heterodimeric molecules that are designed to bind simultaneously with two different proteins to form ternary complexes. These heterodimeric molecules often display compelling biological activity; however, they are difficult to characterize. The bimolecular interaction between one protein and the heterodimeric ligand (primary dissociation constant) can be determined by a number of methods. However, the interaction between that protein-ligand complex and the second protein (secondary dissociation constant) is more difficult to measure due to the noncovalent nature of the original protein-ligand complex. Consequently, these heterodimeric compounds are often characterized in terms of their activity, which is an experimentally dependent metric. We have developed a general quantitative mathematical model that can be used to measure both the primary (protein + ligand) and secondary (protein-ligand + protein) dissociation constants for heterodimeric small molecules. These values are largely independent of the experimental technique used and furthermore provide a direct measure of the thermodynamic stability of the ternary complexes that are formed. Fluorescence polarization and this model were used to characterize the heterodimeric molecule, **SLFPYEEI**, which binds to both FKBP12 and the Fyn SH2 domain, demonstrating that the model is useful for both predictive as well as ex post facto analytical applications.

CC Mathematical biology and statistical methods 04500

Biochemistry studies - General 10060

Biophysics - Biocybernetics 10515

IT Major Concepts

Biochemistry and Molecular Biophysics; Methods and Techniques; Models and Simulations (Computational Biology)

IT Chemicals & Biochemicals

FKBP12; Fyn: SH2 domain; **SLFPYEEI**: heterodimeric molecule; protein-ligand complex; ternary complex

IT Methods & Equipment

biophysical analysis: laboratory techniques; fluorescence polarization: laboratory techniques, spectrum analysis techniques; quantitative analysis: mathematical and computer techniques; quantitative mathematical model: laboratory equipment

IT Miscellaneous Descriptors

intermolecular binding; thermodynamic stability

ANSWER 1 OF 2 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

DUPLICATE 1

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Biochemistry studies - General 10060

Biophysics - Biocybernetics 10515

IT Major Concepts

Biochemistry and Molecular Biophysics; Methods and Techniques; Models and Simulations (Computational Biology)

IT Chemicals & Biochemicals

FKBP12; Fyn: SH2 domain; **SLFPYEEI**: heterodimeric molecule; protein-ligand complex; ternary complex

IT Methods & Equipment

biophysical analysis: laboratory techniques; fluorescence polarization: laboratory techniques, spectrum analysis techniques; quantitative analysis: mathematical and computer techniques; quantitative mathematical model: laboratory equipment

IT Miscellaneous Descriptors

intermolecular binding; thermodynamic stability

AN 2000:802773 CAPLUS  
 DN 134:125901  
 ED Entered STN: 15 Nov 2000  
 TI Mechanistic studies of affinity modulation  
 AU Rosen, Michael K.; Amos, Christopher D.; Wandless, Thomas J.  
 CS Department of Chemistry, Stanford University, Stanford, CA, 94305, USA  
 SO Journal of the American Chemical Society (2000), 122(48), 11979-11982  
 CODEN: JACSAT; ISSN: 0002-7863  
 PB American Chemical Society  
 DT Journal  
 LA English  
 CC 1-12 (Pharmacology)  
 Section cross-reference(s): 6  
 AB A synthetic ligand for the protein FKBP12 was covalently linked to a peptide ligand (pYEEI) for the Fyn SH2 protein to create a bifunctional mol. called **SLFpYEEI**. This bifunctional mol. can simultaneously bind both proteins to form a trimeric complex. When **SLFpYEEI** is precomplexed with FKBP12, the peptide ligand binds 6-fold more weakly to the Fyn SH2 domain than **SLFpYEEI** alone. Isotope-edited NMR spectroscopy was used to investigate the mol. basis for the observed reduction in affinity. The results suggest that interactions between the pYEEI peptide and FKBP12 may play a significant role in diminishing the affinity of **SLFpYEEI** for the Fyn SH2 domain.  
 ST FKBP12 peptide ligand protein drug design  
 IT Proteins, specific or class  
 RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
 (FKBP-12 (FK 506-binding protein, 12,000-mol.-weight); mechanistic studies of affinity modulation)  
 IT Protein motifs  
 (SH2 domain; mechanistic studies of affinity modulation)  
 IT Drug design  
 (mechanistic studies of affinity modulation)  
 IT 225108-46-3  
 RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
 (mechanistic studies of affinity modulation)  
 RE.CNT 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 RE  
 (1) Amzel, L; Current Opin Biotechnol y 1998, V9, P366 CAPLUS  
 (2) Atwell, S; Science 1997, V278, P1125 CAPLUS  
 (3) Briesewitz, R; Proc Natl Acad Sci U S A 1999, V96, P1953 CAPLUS  
 (4) Carson, M; J Appl Crystallogr 1991, V24, P958  
 (5) Cohen, G; Cell 1995, V80, P237 CAPLUS  
 (6) Delaglio, F; J Biomol NMR 1995, V6, P277 CAPLUS  
 (7) Delano, W; Science 2000, V287, P1279 CAPLUS  
 (8) Holt, D; J Am Chem Soc 1993, V115, P9925 CAPLUS  
 (9) Johnson, B; J Biomol NMR 1994, V4, P603 CAPLUS  
 (10) Kay, L; J Am Chem Soc 1992, V114, P10663 CAPLUS  
 (11) Kay, L; J Magn Reson Ser A 1994, V109, P129 CAPLUS  
 (12) Meadows, R; Biochemistry 1993, V32, P754 CAPLUS  
 (13) Michnick, S; Science 1991, V252, P836 CAPLUS  
 (14) Mulhern, T; Structure 1997, V5, P1313 CAPLUS  
 (15) Pawson, T; Genes Develop 2000, V14, P1027 CAPLUS  
 (16) Pawson, T; Nature 1995, V373, P573 CAPLUS  
 (17) Rajagopal, P; Protein Sci 1997, V6, P2624 CAPLUS  
 (18) Rosen, M; Biochemistry 1991, V30, P4774 CAPLUS  
 (19) Sheinerman, F; Current Opin Struct Biol 2000, V10, P153 CAPLUS  
 (20) Smithgall, T; J Pharmacol Toxicol Methods 1995, V34, P125 CAPLUS  
 (21) Xu, R; Biopolymers 1993, V33, P535 CAPLUS  
 (22) Zhang, O; J Biomol NMR 1994, V4, P845 CAPLUS

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RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)  
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IT Protein motifs  
(SH2 domain; mechanistic studies of affinity modulation)  
IT Drug design  
(mechanistic studies of affinity modulation)  
IT 225108-46-3  
RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)  
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(3) Briesewitz, R; Proc Natl Acad Sci U S A 1999, V96, P1953 CAPLUS  
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(6) Delaglio, F; J Biomol NMR 1995, V6, P277 CAPLUS  
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(13) Michnick, S; Science 1991, V252, P836 CAPLUS  
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updated Search  
WCOOK 4/7/06  
09/7/16,054

d his

(FILE 'HOME' ENTERED AT 10:55:34 ON 07 APR 2006)

FILE 'BIOSIS, CAPLUS, EMBASE, MEDLINE' ENTERED AT 10:55:49 ON 07 APR 2006

L1	455 S (5000 DALTONS)
L2	63 S L1 AND BIND?
L3	45 DUPLICATE REMOVE L2 (18 DUPLICATES REMOVED)
L4	27 S L3 AND PROTEIN?
L5	25 S L4 AND PD<2000

AN 1990:2184 CAPLUS  
DN 112:2184  
ED Entered STN: 06 Jan 1990  
TI Metal-**protein** interactions in transport, accumulation, and excretion of metals  
AU Sarkar, Bibudhendra  
CS Res. Inst., Hosp. Sick Child., Toronto, ON, M5G 1X8, Can.  
SO Biological Trace Element Research (1989), Volume Date 1988, 21, 137-44  
CODEN: BTERDG; ISSN: 0163-4984  
DT Journal  
LA English  
CC 4-3 (Toxicology)  
AB The **binding** of Cu(II), Zn(II), Ni(II), and Cd(II) to **protein** components in serum, placenta, kidney, and urine was investigated at physiol. pH, using radioisotopes as tracers. All the four metals were bound to albumin and other macromols. in serum. However, small amts. were also bound to low mol. weight components of the size 1500-10,000 daltons. The nature of the Cu(II)-**binding** to  $\alpha$ -fetoprotein suggests its important role as the Cu(II)-transporting **protein** in fetal life. Metal **binding** to placental components were studied using both rat placenta and isolated human trophoblast cells. Studies of metal **binding** targets in kidney resulted in the isolation of a 4000 daltons acidic polypeptide which **binds** Ni(II) and Cd(II) with  $K_{app} = 1.1 \times 10^{-5}$  and  $2.3 \times 10^{-5}$ , resp. Studies of metal **binding** substances in urine reveals the major amts. of these metals **binding** to substances of mol. weight 500-5000 daltons. Preliminary amino acid anal. suggests that these components are rich in acidic amino acids, similar to what has been found with kidney polypeptide. There may be a general role for such compds. in the handling of metals in the process of excretion.  
ST heavy metal **protein** transport excretion  
IT Albumins, biological studies  
RL: BIOL (Biological study)  
(heavy metals **binding** by, urinary excretion in relation to)  
IT Urine  
(heavy metals excretion in, interaction with **proteins** in relation to)  
IT Placenta  
(**proteins** of, heavy metals interaction with)  
IT Kidney, composition  
(**proteins** of, heavy metals interaction with, urinary excretion in relation to)  
IT **Proteins**, specific or class  
RL: BIOL (Biological study)  
(low-mol.-weight, of blood and kidney, heavy metals interaction with, urinary excretion in relation to)  
IT Trace elements, biological studies  
RL: BIOL (Biological study)  
(metals, heavy, **binding** of, by blood **proteins**, urinary excretion in relation to)  
IT Fetoproteins  
RL: BIOL (Biological study)  
( $\alpha$ -, heavy metals **binding** by)  
IT 7440-02-0, Nickel, biological studies 7440-43-9, Cadmium, biological studies 7440-50-8, Copper, biological studies 7440-66-6, Zinc, biological studies  
RL: BIOL (Biological study)  
(**binding** of, by blood **proteins**, urinary excretion in relation to)

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DN 112:2184  
ED Entered STN: 06 Jan 1990  
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ST heavy metal **protein** transport excretion  
IT Albumins, biological studies  
RL: BIOL (Biological study)  
(heavy metals **binding** by, urinary excretion in relation to)  
IT Urine  
(heavy metals excretion in, interaction with **proteins** in relation to)  
IT Placenta  
(**proteins** of, heavy metals interaction with)  
IT Kidney, composition  
(**proteins** of, heavy metals interaction with, urinary excretion in relation to)  
IT **Proteins**, specific or class  
RL: BIOL (Biological study)  
(low-mol.-weight, of blood and kidney, heavy metals interaction with, urinary excretion in relation to)  
IT Trace elements, biological studies  
RL: BIOL (Biological study)  
(metals, heavy, **binding** of, by blood **proteins**, urinary excretion in relation to)  
IT Fetoproteins  
RL: BIOL (Biological study)  
( $\alpha$ -, heavy metals **binding** by)  
IT 7440-02-0, Nickel, biological studies 7440-43-9, Cadmium, biological studies 7440-50-8, Copper, biological studies 7440-66-6, Zinc, biological studies  
RL: BIOL (Biological study)  
(**binding** of, by blood **proteins**, urinary excretion in relation to)



## ANSWER 9 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1997:544355 CAPLUS  
 DN 127:187865  
 ED Entered STN: 27 Aug 1997  
 TI Noncompetitive immunoassay with blocking of unoccupied specific  
**binding** sites on solid phase  
 IN Saviranta, Petri  
 PA Wallac Oy, Finland; Orion-Yhtymä Oy; Saviranta, Petri  
 SO PCT Int. Appl., 23 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 IC ICM G01N033-543  
 ICS G01N033-53  
 CC 9-10 (Biochemical Methods)  
 Section cross-reference(s): 1, 2, 15

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9729373	A1	19970814	WO 1997-FI59	19970204 <--
	W: JP, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	FI 9600534	A	19970807	FI 1996-534	19960206 <--
	FI 100276	B1	19971031		
	EP 886754	A1	19981230	EP 1997-902373	19970204 <--
	EP 886754	B1	20030122		
	R: DE, FR, GB				
	US 6037185	A	20000314	US 1998-101358	19980708
PRAI	FI 1996-534	A	19960206		
	WO 1997-FI59	W	19970204		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 9729373	ICM	G01N033-543
	ICS	G01N033-53
	IPCI	G01N0033-543 [ICM,6]; G01N0033-53 [ICS,6]
	IPCR	G01N0033-536 [I,A]; G01N0033-536 [I,C]; G01N0033-543 [I,A]; G01N0033-543 [I,C]; G01N0033-74 [I,A]; G01N0033-74 [I,C] <--
FI 9600534	IPCI	G01N0033-53 [ICM,6]; G01N0033-74 [ICS,6]; G01N0033-88 [ICS,6]; G01N0033-94 [ICS,6]; G01N0033-543 [ICS,6] <--
EP 886754	IPCI	G01N0033-53 [ICM,7]; G01N0033-543 [ICS,7]; G01N0033-74 [ICS,7]
	IPCR	G01N0033-536 [I,A]; G01N0033-536 [I,C]; G01N0033-543 [I,A]; G01N0033-543 [I,C]; G01N0033-74 [I,A]; G01N0033-74 [I,C] <--
US 6037185	IPCI	G01N0033-566 [ICM,7]; G01N0033-557 [ICS,7]; C12Q0001-68 [ICS,7]; A61K0039-395 [ICS,7]
	IPCR	G01N0033-536 [I,A]; G01N0033-536 [I,C]; G01N0033-543 [I,A]; G01N0033-543 [I,C]; G01N0033-74 [I,A]; G01N0033-74 [I,C]
	NCL	436/500.000; 435/004.000; 435/006.000; 435/007.100; 435/007.600; 435/007.800; 435/007.900; 435/007.920; 435/007.940; 435/007.950; 436/501.000; 436/503.000; 436/504.000; 436/517.000; 436/518.000; 436/523.000; 436/524.000; 436/528.000; 436/533.000; 436/537.000; 436/541.000; 436/542.000; 436/543.000; 436/544.000; 436/545.000; 436/546.000
	ECLA	G01N033/536; G01N033/543B; G01N033/74B

AB The present invention relates to a noncompetitive method for the determination  
 of  
 analytes, and especially low-mol.-weight analytes <5000 Daltons  
 (e.g., steroids, vitamins, drugs, drugs of abuse, antibiotics,  
 environmental pollutants, toxins, etc.). Initially the analyte is bound

ANSWER 9 OF 25 CAPLUS COPYRIGHT 2006 ACS on STN

AN 1997:544355 CAPLUS

DN 127:187865

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TI Noncompetitive immunoassay with blocking of unoccupied specific  
**binding** sites on solid phase

IN Saviranta, Petri

PA Wallac Oy, Finland; Orion-Yhtymä Oy; Saviranta, Petri

SO PCT Int. Appl., 23 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM G01N033-543

ICS G01N033-53

CC 9-10 (Biochemical Methods)

Section cross-reference(s): 1, 2, 15

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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9729373	A1	19970814	WO 1997-FI59	19970204 <--
	W: JP, US				
	RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	FI 9600534	A	19970807	FI 1996-534	19960206 <--
	FI 100276	B1	19971031		
	EP 886754	A1	19981230	EP 1997-902373	19970204 <--
	EP 886754	B1	20030122		
	R: DE, FR, GB				
	US 6037185	A	20000314	US 1998-101358	19980708
PRAI	FI 1996-534	A	19960206		
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CLASS

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WO 9729373	ICM	G01N033-543
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	IPCR	G01N0033-536 [I,A]; G01N0033-536 [I,C]; G01N0033-543 [I,A]; G01N0033-543 [I,C]; G01N0033-74 [I,A]; G01N0033-74 [I,C] <--
FI 9600534	IPCI	G01N0033-53 [ICM,6]; G01N0033-74 [ICS,6]; G01N0033-88 [ICS,6]; G01N0033-94 [ICS,6]; G01N0033-543 [ICS,6] <--
EP 886754	IPCI	G01N0033-53 [ICM,7]; G01N0033-543 [ICS,7]; G01N0033-74 [ICS,7]
	IPCR	G01N0033-536 [I,A]; G01N0033-536 [I,C]; G01N0033-543 [I,A]; G01N0033-543 [I,C]; G01N0033-74 [I,A]; G01N0033-74 [I,C] <--
US 6037185	IPCI	G01N0033-566 [ICM,7]; G01N0033-557 [ICS,7]; C12Q0001-68 [ICS,7]; A61K0039-395 [ICS,7]
	IPCR	G01N0033-536 [I,A]; G01N0033-536 [I,C]; G01N0033-543 [I,A]; G01N0033-543 [I,C]; G01N0033-74 [I,A]; G01N0033-74 [I,C]
	NCL	436/500.000; 435/004.000; 435/006.000; 435/007.100; 435/007.600; 435/007.800; 435/007.900; 435/007.920; 435/007.940; 435/007.950; 436/501.000; 436/503.000; 436/504.000; 436/517.000; 436/518.000; 436/523.000; 436/524.000; 436/528.000; 436/533.000; 436/537.000; 436/541.000; 436/542.000; 436/543.000; 436/544.000; 436/545.000; 436/546.000
	ECLA	G01N033/536; G01N033/543B; G01N033/74B

AB The present invention relates to a noncompetitive method for the determination  
of

analytes, and especially low-mol.-weight analytes <5000 Daltons  
(e.g., steroids, vitamins, drugs, drugs of abuse, antibiotics,  
environmental pollutants, toxins, etc.). Initially the analyte is bound

to a specific **binding** partner, after which the unoccupied **binding** sites of the **binding** partner are inactivated. The bound analyte is then dissociated from the **binding** partner and replaced by a labeled marker, after which the bound labeled marker is determined. The signal from the bound labeled marker is directly proportional to the initial amount of analyte in the sample, which makes the present method more favorable than the competitive assays. The invention is illustrated by the determination of 17 $\beta$ -estradiol.

ST noncompetitive immunoassay unoccupied **binding** site blocking;  
estradiol detn noncompetitive immunoassay; drug detn noncompetitive immunoassay

IT Macromolecular compounds

RL: ARG (Analytical reagent use); BPR (Biological process); BSU (Biological study, unclassified); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)  
(biol.; noncompetitive immunoassay with unoccupied **bindi**

to a specific **binding** partner, after which the unoccupied **binding** sites of the **binding** partner are inactivated. The bound analyte is then dissociated from the **binding** partner and replaced by a labeled marker, after which the bound labeled marker is determined. The signal from the bound labeled marker is directly proportional to the initial amount of analyte in the sample, which makes the present method more favorable than the competitive assays. The invention is illustrated by the determination of 17 $\beta$ -estradiol.

ST noncompetitive immunoassay unoccupied **binding** site blocking;  
estradiol detn noncompetitive immunoassay; drug detn noncompetitive immunoassay

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FILE 'BIOSIS, CAPLUS, EMBASE, MEDLINE' ENTERED AT 10:55:49 ON 07 APR 2006

L1	455 S (5000 DALTONS)
L2	63 S L1 AND BIND?
L3	45 DUPLICATE REMOVE L2 (18 DUPLICATES REMOVED)
L4	27 S L3 AND PROTEIN?
L5	25 S L4 AND PD<2000

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